J Med Genet 1994;31:126–129

Facial clefts in the west of Scotland in the period 1980–1984: epidemiology and genetic diagnoses

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Abstract

Two hundred and eighty six cases of cleft lip, cleft palate, or both were identified in a study attempting complete ascertainment of babies with facial clefts born to women resident in the west of Scotland in a five year period beginning 1 January 1980. The total birth prevalence (TBP) of these defects over this period was 1·53 per 1000. The TBP for cleft lip with or without cleft palate (CL[P] was 0·74 per 1000 and for cleft palate (CP) was 0·79 per 1000; 26% of CL[P] and 39·5% of CP cases had one or more major congenital anomaly associated with their facial cleft and in over half of these cases a specific genetic or syndrome diagnosis could be made. In comparison to previous European reports this study shows a high incidence of associated abnormalities and a remarkably low ratio of CL[P]:CP cases.

(J Med Genet 1994;31:126–129)

Cleft lip with or without cleft palate (CL[P] and cleft palate (CP) are aetiologically distinct subgroups of the facial cleft group of anomalies. This distinction has been made on the basis of the different embryological timings of primary and secondary palate closure[1] and recurrence of the same type of defect within a family.[2–5] There are also epidemiological differences between the groups which include an observed racial variation in the birth prevalence of CL[P][6–9] but not CP,[9 10] an excess of male cases in most reports of the CL[P] group,[2 4 10 11] and a slight female excess in the CP group.[10 12] The higher incidence of associated congenital anomalies that has been reported in subjects with CP compared to those with CL[P][13 14] has also been cited as evidence of distinct aetiologies for these groups.

In spite of the differences between these groups there is evidence suggesting common factors in their aetiology. Woolf[15] has shown a small but convincing increase in the occurrence of CP in the families of a large cohort of patients with CL[P]. Rintala[16] reported a remarkable parallelism in the changes of birth prevalence of CL[P] and CP over a 27 year period in the Finnish population. It has also been noted that families with Van der Woude syndrome (MIM 119300) may have both types of defect associated with lip pits segregating in one pedigree.[17] Finally, a variation in the transforming growth factor α (TGFα) gene has been found to be over-represented in cohorts of unrelated subjects with both CL[P] and CP.[18–21]

Previous reports of facial clefts in Scotland[22 23] have suggested that there is a relatively low incidence of CL[P] and high incidence of CP in this population compared to the European average. In the present study we have attempted complete ascertainment of babies born with facial clefts, within a five year period, to mothers living in the west of Scotland in order to calculate the birth prevalence of each subgroup. Particular attention was paid during the study to the number and nature of associated congenital anomalies and the specific genetic diagnosis in each of the subgroups. Data derived from this study are compared to those reported in other studies of European populations.

Materials and methods

The study population comprised those infants born to mothers whose main residence was within Greater Glasgow, Lanarkshire, Forth Valley, Dumfries and Galloway, Argyll and Clyde, or Ayrshire and Arran Health Boards from 1 January 1980 to 31 December 1984. The index cases were identified through four main sources; neonatal discharge forms, hospital admission records, the Glasgow database for European Registration for Congenital Anomalies and Twins (EUROCAT), and hospital diagnostic indices. Follow up information on index cases with associated abnormalities was obtained from personal examination, hospital records, genetic records, and detailed necropsy reports.

Patients with microforms of facial clefts (bifid uvula and submucous cleft palate) were excluded from the study group as the majority of these defects do not come to medical attention and would, therefore, require a population survey for complete ascertainment.[24 25]

A figure for birth prevalence was calculated, as the common occurrence of facial clefts in early spontaneous abortions[26] would make an incidence of these defects very difficult to estimate. Birth prevalence figures were calculated per 1000 total births (‰TB) or live births (‰LB) and quoted with 95% confidence intervals using the methods of Czeizel and Tusnady.[27] Groups were compared using the χ^2 test and the Yates correction factor was used in the two by two contingency tables ($YM\chi^2$). Evidence of cyclical trends within the facial clefts groups were assessed using both parametric[28] and non-parametric rank sum[29] methods. Associated congenital anomalies were assigned to major and minor categories using the guidelines of Smith.[30]

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Received 25 May 1993
Revised version accepted for publication 17 September 1993

Table 1 Birth prevalence of facial cleft subgroups

Facial cleft	*Total births*	*TBP*	*Live births*	*LBP*
CL[P]	139	0·74 (0·12)	126	0·68 (0·12)
CL	51	0·27 (0·08)	51	0·27 (0·08)
CLP	88	0·47 (0·10)	75	0·41 (0·10)
CP	147	0·79 (0·13)	142	0·78 (0·13)
Total	286	1·53 (0·18)	268	1·44 (0·18)

CL = cleft lip only; CLP = cleft lip with cleft palate; CL[P] = cleft lip with or without cleft palate; CP = cleft palate only; TBP = birth prevalence per 1000 total births (SD 2); LBP = birth prevalence per 1000 live births (SD 2).

Results

BIRTH PREVALENCE (TABLE 1)

Two hundred and eighty six patients with CL[P] or CP were identified among the 187 321 total births in the study population. The total birth prevalence (TBP) was thus estimated as $1{\cdot}53 \pm 0{\cdot}18^{o}/_{oo}$. Cleft lip occurred in 51/286 (17·8%) of the cases, 88/286 (30·8%) had cleft lip and palate (CLP), and 147/286 (51·4%) had CP; 268/286 (93·7%) of the facial cleft cases and 186 139/187 321 (99·4%) of total births were liveborn, so the live birth prevalence (LBP) can be calculated as $1{\cdot}44 \pm 0{\cdot}18^{o}/_{oo}$. Of the liveborn patients 51/268 (19·0%) had CL, 75/268 (28·0%) had CLP, and 142/268 (53·0%) had CP.

NATURE OF CLEFT LIP DEFECT

Of the 139 cases of CL[P] identified, 51/139 (36·7%) had CL and 88/139 (63·3%) had CLP; 86/139 (61·9%) had unilateral defects, two cases had midline defects (1·4%), and in 41/139 (29·5%) the defect was bilateral. In 10 cases (7·2%) the nature of the lip defect was not recorded. In the unilateral CL[P] cases (where laterality was recorded) left sided defects were significantly more common, accounting for 55/86 (63·9%) of this group ($\chi^2 = 6{\cdot}7$, $p < 0{\cdot}01$).

SEX DIFFERENCES (TABLE 2)

There was a statistically significant excess of males (90/139, 64·7%) among all CL[P] cases ($YM\chi^2 = 8{\cdot}36$, $p < 0{\cdot}01$) giving a male:female ratio (m:f) of 1·84:1. This difference was almost entirely because of the male excess in CL[P] cases with no associated abnormalities (m:f = 74:29, $YM\chi^2 = 18{\cdot}8$, $p << 0{\cdot}01$). In the CP group 81/147 (55·1%) of all cases were female (m:f = 0·81:1, $YM\chi^2 = 3{\cdot}11$, $p > 0{\cdot}05$). Interestingly, the female excess in the CP group was most prominent in CP cases without associated abnormalities (m:f = 0·65:1) and in cases with Pierre-Robin sequence (PRS) without additional abnormalities (m:f 0·36:1). These differences were not statistically significant.

Table 2 Sex distribution in the facial cleft subgroups

Facial cleft	*ICA Male*	*ICA Female*	*MCA Male*	*MCA Female*
CL[P]	74*	29	16	20
CL	35*	11	3	2
CLP	39*	18	13	18
CP (total)	35	54	31	27
Pierre-Robin sequence (PRS)	5	14	4	0
CP (excl PRS)	30	40	27	27

* Highly significant excess of male cases ($p < 0{\cdot}01$); CL = cleft lip only; CLP = cleft lip with cleft palate; CL[P] = cleft lip with or without cleft palate; CP = cleft palate only; ICA = cases in which the facial cleft was an isolated congenital anomaly; MCA = cases in which the facial cleft was associated with another major congenital anomaly.

GEOGRAPHICAL AND SEASONAL DISTRIBUTION OF BIRTHS

Case distribution assessed by the Health Board of residence of the mother at the time of birth showed no statistically significant differences in TBP or LBP. There was no evidence of significant seasonal variation or cyclical trend in either group (data not shown).

OUTCOME

Thirteen of 139 (9·3%) cases in the CL[P] group were stillborn; 10/126 (7·9%) liveborn CL[P] cases had died by 1 January 1990; 8/10 had major associated anomalies; 5/147 (3·4%) cases in the CP group were stillborn; 14/142 (9·7%) of the liveborn children with CP had died by 01/01/90 and all had major associated abnormalities. The proportions of stillbirths and early deaths were not significantly different in the two groups.

ASSOCIATED ABNORMALITIES

Thirty six of 139 (25·9%) of the CL[P] group and 58/147 (39·5%) of the CP group had one or more major congenital anomaly associated with their facial cleft. Minor congenital anomalies were present in an additional 12/139 (8·6%) CL[P] and 28/147 (19%) CP cases. Single gene defects, chromosomal aberrations and identifiable malformation syndromes accounted for 5·7%, 3·6% and 5·7% in the CL[P] group and 8·2%, 5·4%, and 20·4% in the CP group respectively. In only one CP case was a teratogenic agent (ethanol) thought to be responsible for the facial cleft. A further 17/139 (12·2%) in the CL[P] group and 22/147 (14·8%) of the CP group had associated major malformations that could not be identified as part of a particular syndrome. The remaining cases (10/48 CL[P] and 14/86 CP) had single associated minor abnormalities. The known diagnoses in both groups are summarised in table 3.

Discussion

Much of the data reported here are similar to those reported from other European populations. In particular, TBP of facial clefts,[2 4 16 31 32] laterality of lip defects,[10 12] sex ratio differences of the subgroups,[10 12] and outcome data[33] are apparently consistent findings that have been the subject of several excellent reviews[10 12 34] and, therefore, will not be discussed further. Our data, however, do differ significantly from previous reports in the proportion of cases with associated major congenital abnormalities (AMCA) and in the relative frequency of CL[P] and CP in the cohort.

Comparing AMCA incidences between studies is difficult owing to the lack of a rigorous definition of terms used to describe such anomalies[35] (for example, uncomplicated micrognathia in Pierre-Robin sequence). However, given these limitations there is a remarkable range in the proportion of cases with AMCA between apparently well ascertained cohorts (table 4, 2·9 to 22·8% for CL[P] and

Table 3 Genetic diagnoses in the facial cleft group

Category	Disorder in CL[P] group	Disorder in CP group
Autosomal dominant	Myotonic dystrophy	Myotonic dystrophy
	Van der Woude syndrome (2)	Van der Woude syndrome
	Hay-Wells syndrome	Stickler syndrome (2)
	Popliteal web syndrome	Ectrodactyly-ectodermal dysplasia-clefting syndrome
	Greig syndrome	Velocardiofacial syndrome
		Treacher Collins syndrome
		Crouzon syndrome
Autosomal recessive	Hypertelorism-microtia-clefting syndrome	Campomelic syndrome
		Diastrophic dysplasia
		Kneist dysplasia
X linked	X linked hydrocephalus	Orofaciodigital type I
Chromosomal	Trisomy 13 (3)	Trisomy 18 (2)
	46,X,+t(10;X)	Trisomy 18 mosaic
	46,XX,3q+	46,XY,9p+
		46,XY,t(3;5;9)+t(6;17)
		45,X,-9-X,+t(9;X)
		46,XY,del(11)(q21-23)
Malformation syndromes	Schisis association (3)	Schisis association (4)
	Holoprosencephaly	Pierre-Robin sequence (23)
	1st/2nd arch syndrome (2)	1st/2nd arch syndrome (2)
	Di George syndrome	VATER association
	Dandy-Walker syndrome	

6·5 to 38·0% for CP) with the present study appearing to have the highest incidence of AMCA (26% CL[P] and 39·5% CP) among the groups chosen for comparison. Possible explanations for these differences will be discussed below. The nature of the AMCA reported in these studies is also of importance when comparing these data and may give clues to the pathogenesis of these disorders. This information has, however, been generally less well documented, presumably because of the heterogeneous nature of these anomalies. In the present study 55% (58% CL[P], 53·5% CP) of the cases with AMCA had a cytogenetic, DNA based, or syndrome diagnosis leaving a significant minority of cases without a specific diagnosis. In a study of 1000 patients referred to a centre specialising in the treatment of craniofacial disorders, Shprintzen *et al*[14] reported similar results with 41% of CL[P] and CP cases with AMCA having no specific diagnosis.

The CL[P]:CP ratio provides a convenient method for observing differences in subgroup distribution between populations. In European populations the average TBP is about $1^{o}/_{oo}$ for CL[P] and $0{\cdot}5^{o}/_{oo}$ for CP[10 12] thus giving a predicted CL[P]:CP ratio of approximately 2. It is evident from the ratios derived from seven widely quoted reports (table 4) that the Scots and the Finns[31] have significantly lower ratios than the rest of the group ($p<0{\cdot}01$). Other Scottish[22 23] and Finnish[13] studies have shown similarly low CL[P]:CP ratios. As the overall TBP in these reports are similar, it would appear that the altered CL[P]:CP ratios in Scotland and Finland are the result of both "too many" CP cases and "too few" CL[P] cases. The CL[P]:CP ratio of those cases with facial cleft as an isolated congenital anomaly (ICA) and those with AMCA were also compared (table 4). The CL[P]:CP ratio in the ICA group in all the studies was found to be higher than that in either the combined group or the AMCA group; however, the ratio in the Finns and the Scots remain significantly below the European average ($p<0{\cdot}01$). Interestingly, the ICA CL[P]:CP ratio from the Hungarian population[5] appears to be significantly higher ($p<0{\cdot}01$) than other reports.

There are three possible explanations for these results, none of which is mutually exclusive. Firstly the results could be artefactual, secondly, a specific environment influences the numbers of cases with AMCA and the CL[P]:CP ratio, and, thirdly, the differences are because of the populations being genetically heterogeneous. The studies chosen for comparison (table 4) used standard, multiple source techniques of ascertainment and were carried out by respected investigators so it would seem unlikely that the observed differences are the result of biased ascertainment.

Evidence that environmental or genetic factors or both may influence the CL[P]:CP ratio comes from a study in which Beckman and Myrberg[37] observed that it varied inversely with latitude in Sweden. They found the ratio to be 1·46:1 in northern counties, 1·82:1 in central counties, and 3·72:1 in southern counties with similar TBP in each group. Thus the factors acting on the Scottish and Finnish populations producing low CL[P]:CP ratios may be a result of their location in northern latitudes. The lack of seasonal variation in both the present study and previous reports,[39 40] however, implies that any exogenic factors acting on these populations are not directly related to temperature, weather, or daylight effects. Although the identification of specific environmental factors acting on populations has proven difficult, the reduction in recurrence of facial clefts born to women who had taken periconceptional multivitamin supplementation[41] may suggest an aetiological or corresponding role for dietary factors.

The regional differences in CL[P]:CP ratio and the proportion of facial cleft cases with AMCA could also reflect genetic differences in these populations. The prospect of elucidating such hereditary factors involved in facial clefting has been enhanced by the discovery of an association between both isolated CL[P] and

Table 4 CL[P]:CP ratios in European populations

Study population	Year	TBP	Total No CL[P]:CP cases	CL[P]:CP ratio	No of cases with AMCA CL[P]:CP	CL[P]:CP ratio of cases without AMCA
English[32]	1962	1·42	386:188	2·05	20:23	2·21
Canadian[36]*	1969	1·63	493:244	2·02	NR	—
Swedish[37]	1972	1·72	296:140	2·11	NR	—
Finnish[31]	1974	1·69	289:298	0·97	57:66	1·00
Hungarian[5]	1980	1·67	1407:588	2·39	321:223	2·97
French[4]	1982	1·52	121:71	1·71	17:27	2·36
Danish[38]	1988	1·88	492:186	2·65	14:12	2·74
Scottish†	1992	1·53	139:147	0·94	36:58	1·16

* These data refer to white (non-Indian) cases. †Present study. TBP = birth prevalence per 1000 total births. CL[P] = cleft lip with or without cleft palate. CP = cleft palate only. AMCA = associated major congenital anomalies.

CP and a genetic variation in the TGF α gene.[18–21] It may be possible in the future to show genetic differences between facial cleft groups in different populations that will explain the CL[P]:CP ratio using this or other candidate gene probes. We are currently undertaking such a study in our population.

In conclusion, we cannot explain the differences in subgroup ratios and associated abnormalities found in European populations; however, it would appear that the commonly held assumption that there is little or no variation in the birth prevalence of CP[9 10] is incorrect. To advance our understanding of the constellation of abnormalities that are associated with facial clefts it will be necessary to collect a large, well documented cohort of patients with facial clefts as part of multiple congenital anomalies in the hope that new diagnostic categories could be identified. This will certainly be a useful future role for projects such as the EUROCAT registers. Facial clefts have been one of the most intensely studied of human malformations with almost every report raising more questions than it has answered. This study follows the tradition and we hope that it will stimulate further research.

We would like to thank Drs John Tolmie and Rosemarie Davidson for their invaluable help with syndrome identification and Dr David Stone for access to information stored on the Glasgow EUROCAT register and Dr Susan Cole (CSA, Trinity House, Edinburgh) for access to the SMR database information.

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